

PREAMBLE

Many clinically important drugs, such as aspirin, digitoxin, progesterone, cortison and morphine, have been derived directly or indirectly from higher plants. Less well-recognised but of great clinical importance are the widely used drugs from fungi such as the antibiotics, penicillin and griseofulvin, the ergot alkaloids and cyclosporin.

During the last two decades there has been an increasing recognition of the role of the human immune system for maintaining good health. Diseases now associated with immune dysfunction such as cancer, chronic fatigue syndrome, AIDS/HIV, hepatitis and autoimmune conditions are increasingly coming to the forefront and being given special attention from medical researchers and clinicians alike. Historically, the larger fungi, the mushrooms, have had a long and successful medicinal use especially in traditional Chinese clinical medicine for many forms of immune disorders. Chinese Pharmacopeias document the use of well over 100 species of mushroom by practitioners of traditional Chinese medicine, for a wide range of ailments. Many of these mushroom-derived medicinal products are now produced by major Japanese, Korean and Chinese pharmaceutical companies. Many of these products are being used worldwide by holistically oriented physicians, chiropractors, herbalists and naturopathic physicians in a clinical environment. To date, Western, medicine has made little use of these products in part due to their complex structure and lack of acceptable pharmaceutical purity.

Mushrooms are not a taxonomic group but do include well over 12,000 species which have macroscopic fruit-bodies, the mushrooms, which are large enough to be seen by the naked eye. Mushrooms are increasingly being evaluated in the West for their nutritional value and acceptability as well as their

pharmacological properties. Increasingly, many are being viewed nutritionally as functional foods as well as a source of physiologically beneficial and non-invasive medicines, while others are distinctly non-edible but considered purely as a source of medicinally beneficial compounds. Some of the most recently isolated and identified compounds originating from the medicinal mushrooms have shown promising immunomodulatory, antitumour, cardiovascular, antiviral, antibacterial, antiparasitic, hepatoprotective and antidiabetic properties. Modern scientific studies of the medicinal mushrooms have expanded exponentially during the last two decades primarily in Japan, Korea and China but also in the USA and scientific explanations of how these compounds function in the animal and human systems are increasingly appearing in peer-reviewed scientific and medical journals.

Mushroom-derived polysaccharides are now considered as compounds which are able to modulate animal and human immune responses and to inhibit certain tumour growths. While mushroom glucans are mostly non-cytotoxic, the same is not true of glucan-protein complexes. All of these compounds, however, have been shown to potentiate the host's innate (non-specific) and acquired (specific) immune responses and activate many kinds of immune cells that are important for the maintenance of homeostasis, *e.g.* host cells (such as cytotoxic macrophages, monocytes, neutrophils, natural killer cells, dendritic cells) and chemical messengers (cytokines such as interleukins, interferons, colony stimulating factors) that trigger complement and acute phase responses. Also, they can be considered as multi-cytokine inducers able to induce gene expression of various immunomodulatory cytokines and cytokine receptors. Lymphocytes governing antibody production (β -cells) and cell-mediated cytotoxicity (T-cells) are also

stimulated. However, for most of the mushroom-derived anti-cancer compounds, a detailed understanding of their exact mode of action has not yet been elucidated.

While many mushroom-polysaccharides have been shown to have considerable antitumour activity in several xenographs only a limited number have undergone clinical trials. At present the main products submitted for clinical testing include Lentinan from *Lentinus edodes* fruit-bodies, Schizophyllan from *Schizophyllum commune* mycelial broth, PSK and PSP, from mycelial cultures of *Trametes versicolor* and Grifon-D from fruit-bodies of *Grifola frondosa*. All have been through Phase I, II and III clinical trials mainly in Japan and China but now in US. However, in many cases the standards of these trials may not meet current Western regulatory requirements. In many cases there have been significant improvements in quality of life and survival. Increasingly, several of these compounds are now used extensively in Japan, Korea and China, as adjuncts to standard radio- and chemotherapy. While most of these clinical studies have used extracts from individual medicinal mushrooms, some recent studies from Japan have shown that mixtures of extracts from several known medicinal mushrooms, when taken as a supplement, have shown beneficial effects on the quality of life for some advanced cancer patients.

Perhaps the most encouraging observations from most of these studies is the ability of the mushroom-derived polysaccharides when taken prior to and during radiotherapy and/or chemotherapy to significantly reduce the side-effects of these treatments.

The safety criteria for the mushroom polysaccharides have been exhaustively studied with little evidence of any toxicity. In Phase I clinical trials, these compounds demonstrate remarkably few adverse reactions. Several purified mushroom

polysaccharides have been in clinical use in Japan, Korea, China and more recently in the USA for several years with no reports of any short-term or long-term toxicity.

Clinical efficacy of the mushroom polysaccharides will depend on understanding their precise scope of activity verifiable through *in vitro* and *in vivo* animal and tissue culture tests and human clinical trials, dose range, extraction methods, source and purity of the raw fungal material, duration and frequency of administration, and accuracy in matching the extracts to each particular patient based on traditional and modern diagnostic methods.

This Report, originally commissioned by the Cancer Research Campaign, aims to give a detailed and comprehensive appreciation of this complex area, derived from Oriental and Western literature together with the practical experience of the authors. It is to be hoped that Western oncologists will now have the opportunity to assess this area of cancer treatment and to judge whether it will have a realistic role in Western cancer research programmes.

Finally, from a holistic consideration, the consumption of whole edible medicinal mushrooms or extracts or concentrates (dietary supplements) may well offer novel, highly palatable, nutritious and health benefiting ingredients to the Western diet as functional foods.